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INTERIM PROGRESS REPORT

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STUDIES OF NEUROMUSCULAR FUNCTION

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INTRODUCTION

Using the techniques described in recent reports from this laboratory, investigations are in progress to determine the nature of the block in neuromuscular transmission produced by depolarizing substances such as acetylcholine, which accumulates at the motor end-plate region in anticholinesterase intoxication. The background has been discussed in detail in the Annual Comprehensive Reports dated 30 September 1959 and 31 December 1960.

STUDIES COMPLETED

In vitro application of anticholinesterase compounds to the rat diaphragm preparation as well as to the intercostal muscle preparation as described in Part I of the Annual Comprehensive Report dated 31 December 1960 has been concluded. While the data tended to show that there was a more marked efflux of electrolytes from the muscle in the presence of anticholinesterase inhibition, there was an excessive and non-physiologic efflux in the control muscles. It was, therefore, felt that a transfer of the experimental design in vivo studies would be more meaningful (see below).

STUDIES IN PROGRESS

1. We had had an opportunity to study five patients on extremely large amounts of anticholinesterase medication. In each instance, the patient was suspected some years previously of having myasthenia gravis and was started on anticholinesterase drugs. Subsequent investigation of these patients has revealed that they had no myasthenia. Over the course of the years these patients have been given progressively larger amounts of anticholinesterase medication. For example, one patient was taking 1500 mg. of pyridostigmine daily, while under ordinary circumstances, the normal person may have cholinergic side effects with 60 mg. and serious difficulty with 180 mg. These patients have not been particularly weak, have not had fasciculations or autonomic side effects, nor have they had the classical electromyographic changes of anticholinesterase intoxication despite large doses of these drugs. Investigations of this remarkable tolerance to anticholinesterase medication is currently under way. This phenomena is of interest not only from the standpoint of investigating its nature, but also from the therapeutic implications of the ability of man to develop striking tolerance to not only the muscarinic, but also the nicotinic effects of anticholinesterase intoxication.

2. A parallel investigation is going forward in the experimental animal in which progressively larger doses of anticholinesterase are injected on a daily schedule. Thus far it has been demonstrated that tolerance occurs. At the conclusion of the experimental studies certain animals will be subjected to studies of neuromuscular transmission while others will be utilized for determinations of anticholinesterase LD_{50}. Incidental to this experiment, a

satisfactory semi-micro method for determination of rat whole blood cholinesterase has been developed.

3. The above mentioned study of the mechanism of block produced by anticholinesterase agent has been modified so that anticholinesterase drug is administered in vivo and studies are made of serum and muscle electrolytes, neuromuscular transmission, muscle membrane potential, and end-plate potential. If insignificant changes in serum electrolyte concentration occur, radio-sodium and radio-potassium will be used to determine the efflux rate by the pre-loading technique.

4. Another investigation currently under way in cooperation with the Department of Anesthesiology is the converse of tolerance to anticholinesterase drugs and depolarization, namely, increase susceptibility to the action of depolarizing substances. It has been a clinical finding that an occasional patient will sustain prolonged and respiratory paralysis after administration of depolarizing blocking drugs. In some instances, this may be related to prolonged administration of drug and may be associated with a "late phase" type of block. In other instances, it has been demonstrated that it is due to familial absence of pseudocholinesterase which enhances susceptibility to succinylcholine which requires cholinesterase for its destruction. However, in other instances neither of these mechanisms can be invoked. Investigation of this mechanism is the point of the present study.